

Mild Conversion of Alcohols to Alkyl Halides Using Halide-Based Ionic Liquids at Room Temperature

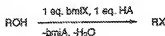
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ABSTRACT



Alcohols were efficiently converted to alkyl halides using 1-*n*-butyl-3-methylimidazolium halides (ionic liquids) in the presence of Brønsted acids at room temperature. The alkyl halide products were easily isolated from the reaction mixture via simple demulsification or extraction, and the 1-*n*-butyl-3-methylimidazolium cation could be recycled for further uses.

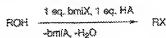
Ionic liquids made of organic cations and appropriate anions are liquids with melting points at or close to room temperature. Ionic liquids have been considered to be the promising remedy for environmental compliance in some industrial processes; therefore, exploration of industrial potential of room-temperature ionic liquids as reaction media has recently become an exciting area of research.¹ Ionic liquids, particularly those based on 1,3-dialkylimidazolium cations, have been shown to be good "solvents" for a wide range of inorganic and organic materials. Without effective vapor pressure they can be employed as nonemissive reaction media from which products can easily be obtained by distillation. On the other hand, immiscibility of ionic liquids with a number of organic solvents provide a solution for biphasic separation of the desired products. This media engineering points to a new frontier of reinventing organic reactions currently practiced in chemical and pharmaceutical industry.

So far ionic liquids are primarily used as solvents/media for organic reactions and other processes such as electrochemical, biochemical, and catalytic processes. However, their utilities as reactants, for example, the capability of the

anions as nucleophiles, have been ignored. Considering that the anions in the absence of other organic solvents may have much enhanced nucleophilicity due to lack of solvation,² it is possible for these ionic liquids to be used as both reaction media and nucleophiles in some organic transformations.

We set out to investigate the conversion of alcohols to alkyl halides in 1,3-dialkylimidazolium halide-based ionic liquids, especially 1-*n*-butyl-3-methylimidazolium halides (bmIX).³ Herein we report our preliminary results on the transformation of alcohols (ROH) to their corresponding alkyl halides (RX) at room temperature using bmIX and Brønsted acids (HA) (Scheme 1). The ionic liquids were recycled in the form of bmIA.

Scheme 1. Conversion of Alcohols to Alkyl Halides in Ionic Liquids



When 1 equiv of 95% sulfuric acid was added to a mixture of *n*-butanol in 1 equiv of 1-*n*-butyl-3-methylimidazolium

(2) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: New York, 1968.

(1) For recent reviews on ionic liquids in green chemistry, see: (a) Carlin, R. T.; Wilkes, J. S. In *Advances in Nonaqueous Chemistry*; Mamturov, G.; Popov, A., Eds.; VCH: New York, 1994. (b) Chowin, Y.; Olivier, H. *ChemTech* 1995, 25, 24. (c) Sedláček, K. R. *J. Chem. Technol. Biotech.* 1997, 68, 351. (d) Olivier, H. *J. Mol. Catal. A: Chem.* 1999, 146, 285. (e) Welton, T. *Chem. Rev.* 1999, 99, 2071. (f) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* 2000, 39, 3772.

bromide (bmBr) at room temperature, a transformation of *n*-butanol to *n*-bromobutane occurred almost quantitatively (entry 5, Table 1). Simple decantation or extraction with

Table 1. Conversion of Alcohols to Alkyl Halides Based on the Reaction in Scheme 1^a

entry	R	X	HA ^b	time (h) ^c	yield (%) ^{d,e}
1	<i>n</i> -butyl	Cl	HCl	>48	N.R. ^f
2	<i>n</i> -butyl	Cl	H ₂ SO ₄	24	35
3	<i>n</i> -butyl	Cl	CH ₃ SO ₃ H	24	98
4	<i>n</i> -butyl	Br	CH ₃ SO ₃ H	24	57
5	<i>n</i> -butyl	Br	H ₂ SO ₄	20 (3)	95 (83)
6	<i>n</i> -butyl	I	H ₂ SO ₄	24 (5)	30 (10)
7	<i>n</i> -butyl	I	CH ₃ SO ₃ H	5	50
8	<i>n</i> -octyl	Cl	H ₂ SO ₄	19	50
9	<i>n</i> -octyl	Cl	CH ₃ SO ₃ H	24	100
10	<i>n</i> -octyl	Br	H ₂ SO ₄	5.5	98 (90 ^g)
11	<i>n</i> -octyl	I	H ₂ SO ₄	22	30
12	<i>n</i> -octyl	I	CH ₃ SO ₃ H	24	70
13	<i>sec</i> -butyl	Cl	CH ₃ SO ₃ H	24	25
14	<i>sec</i> -butyl	Br	H ₂ SO ₄	12 (3)	95 (86)
15	<i>sec</i> -butyl	Br	CH ₃ SO ₃ H	24	15
16	<i>sec</i> -butyl	I	H ₂ SO ₄	24	80
17	<i>sec</i> -butyl	I	CH ₃ SO ₃ H	24	75
18	<i>tert</i> -butyl	Cl	HCl	>48	N.R.
19	<i>tert</i> -butyl	Cl	CH ₃ SO ₃ H	24	25
20	<i>tert</i> -butyl	Br	H ₂ SO ₄	1	85
21	<i>tert</i> -butyl	Br	CH ₃ SO ₃ H	24	16
22	<i>tert</i> -butyl	I	H ₂ SO ₄	24	35
23	<i>tert</i> -butyl	I	CH ₃ SO ₃ H	30	95

^a Notes: All reactions were conducted at room temperature in capped vials at 2 mmol scale using 1 equiv of ionic liquids, 1 equiv of alcohols, and 1 equiv of acids. ^b HCl (37% aqueous), H₂SO₄ (95% aqueous), and neat CH₃SO₃H were used. ^c Numbers in parentheses represent repeated experiments. ^d Yields are based on GC/MS. ^e Isolated yield. ^f N.R. = no reaction.

hexanes was sufficient to achieve the separation of *n*-bromobutane, without further purification. The 1-*n*-butyl-3-methylimidazolium cation was recycled in the form of an ionic liquid (presumably bmBrFSO₃).

This transformation is significant from the viewpoint of pollution avoidance. A widely used method of converting *n*-butanol to *n*-bromobutane involves the heating under reflux of *n*-butanol and sodium bromide (NaBr) in a large excess of concentrated H₂SO₄. The *n*-bromobutane product is then removed azeotropically together with water and unreacted *n*-butanol from the reaction mixture, followed by washing with concentrated H₂SO₄.⁴

We then investigated several classes of alcohol substrates in halide-based ionic liquids using other Brønsted acids. The results are summarized in Table 1. For reason unknown, *n*-butanol and *tert*-butanol failed to react with bmBr when HCl was employed (entries 1 and 18, respectively). However,

by changing to sulfuric acid, *n*-chlorobutane reached 35% conversion in 24 h (entry 2), while methanesulfonic acid gave a quantitative yield (entry 3). When bmBr and methanesulfonic acid were used, *n*-bromobutane formed less efficiently (entry 4) than when H₂SO₄ was used (entry 5). The use of bmBr proved to be troublesome, as the reaction gave rise to a darkened mixture, presumably due to air-oxidation of iodide (entries 6 and 7). The reactions of *n*-octanol followed the same trend (entries 8–12). *sec*-Butanol and *tert*-butanol reacted with various bmBr and acids in the same fashion as *n*-butanol (entries 13–17 and 18–23). It should be pointed out that on the basis of our preliminary results, H₂SO₄ is best suited as the acid reactant to produce alkyl bromides from all three types of alcohols (entries 5, 10, 14, 20), although it seems that tertiary alcohol reacts fastest and secondary alcohol faster than primary alcohol. Methanesulfonic acid appears to be a better choice for the conversion to alkyl chlorides (entries 3, 9, 19) and alkyl iodides (entries 7, 12, 17, 23).

The mechanism is believed to involve protonation of the OH group followed by nucleophilic displacement by halide anions. The proton is presumably in association with either the halide or the conjugate bases of the Brønsted acids used. The rate is accelerated largely because of the ionic liquid media that should aid the charge separation in the transition state. Although it is too early to conclude that mechanisms in our reactions will follow the well-established S_N2, S_N1, or the so-called borderline scenario⁵ for the three types of alkyl alcohols, respectively, the use of ionic liquid reagents/media does present a challenge to the traditionally perceived nucleophilic substitution mechanism.⁶ The ionic liquid reaction media may have a fundamental effect on the reaction kinetics. The predominantly Coulombic force together with the lack of extensive solvation (in a traditional sense) in ionic liquids may exert more important and beneficial influence on the transition state of carbocation character than in nonionic liquid media.

In conclusion, we have demonstrated that the conversion of alkyl alcohols can be efficiently accomplished using 1,3-dialkylimidazolium halide-based ionic liquids and Brønsted acids at room temperature under mild conditions. Further studies on the detailed reaction mechanisms are underway.

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Supporting Information Available: General experimental procedure for conversion of alcohols to alkyl halides and spectra data for isolated 1-bromooctane. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(3) Although bmBr and bmBr are solids at room temperature, warming up or addition of cosolvents such as water can render them liquidlike due to their hydrophilicity.

(4) Nobig, J. R.; Harwood, C. N.; Morrill, T. C.; Neckers, D. C. *Experimental Organic Chemistry*; W. H. Freeman and Company: New York, 1998; p 399.

(5) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A: Structure and Mechanisms*, 4th ed.; Kluwer Academic/Plenum Publishers: New York, 2000; Chapter 5.

(6) A report on ionic liquids as catalytic green solvents for nucleophilic displacement has just appeared. See: Wheeler, C.; West, K. N.; Liotta, C. L.; Eckert, C. A. *Chem. Commun.* 2001, 887.